

Vaccine hesitancy: old story, same mistakes**La vacilación de las vacunas: vieja historia, mismos errores****Hesitação vacinal: velha história, mesmos erros****Natalia Pasternak Taschner¹**

Fear of vaccines is as old as vaccines themselves. Even before Jenner and the smallpox vaccine, people had their questions and concerns about the empirical immunization programs of the time. Back then, inoculating someone with secretions from the pustules of a smallpox patient was already a common practice, but not taken up willingly by many.

The book “The great inoculator: the untold story of Daniel Sutton and his medical revolutions” by Gavin Weightman, gives us a good idea of how the concept of inoculation, and getting someone immunized, was viewed in the 18th century, in a pre-Jenner era¹.

Back then, smallpox was a deadly, feared disease. The death toll was high, with a mortality rate of around 30%, and those who survived were literally scarred for life. Some went blind from the disease. Inoculation was not really a new idea, there are reports of “variolation” - the habit of scraping smallpox pustules from contaminated people and inoculating healthy people with the material - from China since the year 1000. It became regular practice in parts of Asia in the 1600s, and was brought to England by Lady Mary Montagu².

Lady Mary’s ideas were met with great criticism. She had, after all, brought these ideas from Turkey, so there was both religious and sexist prejudice: the method was being proposed by a woman, and had non-Christian origins. But Mary was decided to

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make it work in Britain, having seen how many people in Turkey were protected by inoculation. She had her own son inoculated in Turkey, and her daughter, after their return to England. King George I was not so easily convinced and ordered a “clinical trial”. He had the method tested in prisoners, and after that, on orphaned children. After observing good results, he eventually agreed to have two of his granddaughters inoculated, and after that, people gradually became more reliant on the new method, and inoculation became standard procedure in England too.

Inoculation wasn't perfect, of course, and people died. But overall, it reduced smallpox mortality from 20%-30% to 2%-3%. British doctors, of course, managed to mess public trust in the process with their efforts to “westernize” it and make it fit into the then “modern” western medical paradigm, based on the theory of humors and bloodletting. The simple - and already far from perfect - method of variolation, the simple act of scraping an infected person's pustule and transferring the content to a healthy individual - became tainted with mystic western medicine approaches. The English doctors determined a whole ritual to be performed before the inoculation. This included bloodletting, the use of laxatives and a special diet. Things that did nothing but weaken the patient, and therefore, increase the mortality rate. Mistrust in inoculation began to build.

Mistrust in Science and in health professionals has always been at the core of vaccine hesitancy. When people started to doubt the success of inoculation, merchants of doubt promptly appeared, ready to raise more questions. Religious leaders claimed that inoculation was not according to God's will. It was not for regular people after all, to decide who lives and who dies. Putting the situation into a historical context, we also have to remember that Pasteur and the germ theory wouldn't be around for another couple of centuries, so nobody had any idea how the disease was really transmitted.

Then came Daniel Sutton, and the tide began to change to favor inoculation. Sutton got rid of all the preparedness rituals and performed inoculation much like the Chinese and the Turks, by the simple act of scraping and transferring. He had some good insights, though. It is believed that he deliberately chose as donors' people who had been mildly ill, thus inadvertently selecting milder versions of the virus. It is also said that he chose the recipients among very healthy people, so as to ensure a good survival rate. The result was a very successful inoculation rate, that helped to rebuild trust in the process. In this scenario, comes Jenner, and the vaccination novelty.

Jenner observed that milkmaids rarely got ill with smallpox, and presented few pustules in their hands, from milking the cows. He concluded that the milkmaids were

infected with cowpox, and this was protecting them from getting severely ill with smallpox. He tested his hypothesis on 8-year old James Phipps. After exposing the boy to smallpox several times, Jenner concluded that the process - which became known as vaccination - worked. And it had several advantages to boot! Mortality rate was non-existent compared to the 2%-3% of inoculation, vaccinated people, unlike inoculated people, did not transmit smallpox so there was no need to the usual quarantine required after inoculation. Everything indicated that Jenner's vaccine was sure to become a hit.

Humanity's willingness to embrace change, however, doesn't work like that. People were afraid of the new method. The old method, even if far from perfect, was already known. Jenner's idea was new, and scary. People were afraid of turning into cows, or of having anything coming from a beast inoculated into their bodies. It seemed wrong to mix human and beast, and people hesitated to use the vaccine in their children.

The first antivax movements began to take shape. Anti-vaccination movements and leagues were formed. In the mid 19th century, the first laws enforcing mandatory vaccination were passed, only to be revoked years later due to the pressure of the antivax movements. Publications like "The antivaccinator", and the "Vaccination Inquirer" appeared. People felt deprived of their civil rights, and felt like the State was interfering in what they deemed to be private choices.

Any similarity to the present antivaxer's arguments is no coincidence. Vaccine hesitancy is built on misinformation and lack of trust. It is enhanced by a feeling of liberty lost, and of losing the right to choose. Anti-vaccination movements prey on all these factors. They prey on people's fears, and on people's desire to retain their prerogative to take care of their children as they deem fit. Such movements can be motivated by politics, ideology, or financial gain. Let us not forget that most of vaccine misinformation in the US is propagated by only a dozen people, all connected to selling products, books, and a "natural" way of life where vaccines are viewed as unnecessary and/or harmful³.

Throughout the centuries, vaccine trust has been built, and quite successfully. According to the UNICEF, vaccination today saves 2-3 million children's lives every year. In the world, 45% of all children are protected from deadly diseases, and the number of children with polio has decreased by 99% since 1998⁴.

Despite the worldwide successful vaccination campaigns, and the complete eradication of smallpox, vaccine hesitancy still poses a global threat. The World Health Organization included vaccine hesitancy in the list of the ten global health threats⁵.

Several other incidents throughout history have contributed to increasing vaccine hesitancy. They are usually related to a breach of trust in government institutions, and to misinformation as to how vaccines are manufactured and tested for efficacy and safety. Some historical peaks of antivax movements show that vaccine hesitancy and even the promotion of antivax propaganda are preceded by episodes of miscommunication and/or mishandling of the public trust by scientific or political authorities. The antivax movement is not born in a vacuum, but emerges from a favorable environment built on misinformation and fear.

Take the Cutter incident in the 1960s, for instance. In his book *The Cutter Incident*, Paul Offit guides us through an episode of mistrust in health authorities that probably paved the way to the origins of the modern antivax movement, marked by Andrew Wakefield's fraud paper on the MMR vaccine and autism⁶. The first polio vaccine, by Jonas Salk, using an inactivated virus, had just been approved in the US. Three laboratories were selected to manufacture the vaccine. Eli Lilly and Parker Davis were experienced companies and had been part of the clinical trials. Cutter laboratories wasn't. Offit tells us that Jonas Salk never really delivered detailed instructions on the virus inactivation process, a key step to prevent the vaccine from causing the disease instead of preventing it. Because of this, and also due to a poor regulatory apparatus, whole batches of Cutter's vaccines were actually contaminated with live viruses. The result was 40 thousand children ill with polio, 200 paralyzed, and ten dead.

A decade later, in the 1970s, another hesitancy episode happened, this time involving the tetanus, diphtheria and pertussis vaccine, the DTP. By that time, DTP had been in use in the UK for decades, greatly contributing to defeat these dangerous, typical childhood diseases. The so-called "cellular vaccine" was made up from inactivated *Bordetella pertussis*, and tetanus and diphtheria toxoids. This formulation had strong side effects, sometimes provoking high fever and even convulsions. Reports of vaccine caused encephalopathy started to appear in the British media, and although there was no evidence to actually link these cases to the DTP vaccine, many doctors stopped prescribing and started to advise against vaccination.

The population saw the medical community as "divided" and didn't know who to trust. Misinformation and mistrust of course followed, and again, leagues and associations were formed. Parents of children with encephalopathy were convinced that DTP was the cause of their children's conditions. This type of spurious correlation, that doesn't translate into a cause-and-effect relation, would be explored again by Andrew Wakefield and the purported connection between MMR and autism⁷. The British

government decided to intervene and established an investigative committee to address the issue. The committee concluded that the correlation between DTP and encephalopathy was too weak, and there was no cause-and-effect relation. Even so, it took a major epidemic and an aggressive government campaign to finally convince the British population to get their children vaccinated. The story is best told by Baker and Jeffrey⁸. Today most countries use an acellular formulation of DTP, that causes fewer side effects.

All these stories show how vaccine hesitancy is built from lack of proper communication and a feeling of mistrust in the health authorities. People were afraid of the cowpox vaccine because it was new and came from an animal. People felt cheated because of a grave error in vaccine manufacture during the Cutter incident, and grew suspicious of the attempts made to hide what had happened. A lack of understanding of correlation and causation led medical doctors to spread mistrust and misinformation during the DTP crisis in the UK. And finally, Andrew Wakefield's contention that the MMR vaccine could cause autism was proved to be the result of scientific fraud and corruption⁷ that led to the world's largest antivax movement.

History should teach us not to make the same mistakes. The question that remains during the pandemic is: did we really learn? As scientists, we were so marveled by the Covid19 vaccines clinical trial successes that we forgot that to the general population, they were brand new. The techniques used for the mRNA vaccines, so familiar to anyone who has worked in a microbiology or vaccine lab for the past 30 years, were scary to a lot of people. People were afraid of the genetic vaccines, much as they had been afraid of genetically modified food, two decades ago.

The reason for this fear is the same: no one bothered to explain how vaccines are manufactured and tested for efficacy and safety. We are making the same mistakes repeatedly, and even if in countries like Brazil, vaccine hesitancy is almost nonexistent, the seeds of miscommunication and mistrust are present. Recent episodes involving medical doctors speaking against vaccination take us back to the DTP crisis. Claims of vaccines messing with your DNA, fertility issues, or dangerous side-effects take us back to the pertussis and autism scares. Lack of transparency in communication, with claims of 100% protection for some vaccines, only to make people feel cheated when a vaccinated person eventually becomes ill, or dies. The antivax movement is always ready to prey on fear and mistrust. It only takes a dozen people with good social media skills and the proper environment to do a lot of harm.

People's fears are legitimate and real. They need to be addressed with care, honesty, and transparency. Government health institutions should invest in solid, well designed communication campaigns. Training must be provided to healthcare professionals at the frontline of vaccination campaigns. Medical doctors need to have access and understanding of vaccine's modern manufacturing processes and design, as well as clinical trials.

Covid19 brought about many serious flaws and imperfections in the way different countries deal with vaccination campaigns. Global guidelines for vaccination are urgent, and local interventions and surveys to address national issues. Hopefully we can learn from this global tragedy and rebuild trust in science and vaccines.

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Como citar: Taschner NP. Vaccine hesitancy: old story, same mistakes. J Health NPEPS. 2021; 6(2):e5876.